Clinical Neurology and Neurosurgery 127 (2014) 71–74

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

REM sleep behaviour disorder: How useful is it for the differential diagnosis of parkinsonism?

Renato P. Munhoz[a,*], Helio A. Teive[b]

[a] Movement Disorders Centre, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada
[b] Movement Disorders Unit, Neurology Service, Hospital de Clinicas, Federal University of Parana, Curitiba, Brazil

ARTICLE INFO

Article history:
Received 30 January 2014
Received in revised form 26 August 2014
Accepted 20 September 2014
Available online 5 October 2014

Keywords:
REM sleep behaviour disorder
RBD
Parkinson's disease
Progressive supranuclear palsy
PSP

ABSTRACT

Background: REM sleep behaviour disorder (RBD) is typically linked to synucleinopathies (SP). In this study we analyzed the utility and performance of RBD as a tool for the differential diagnosis of the most common forms of degenerative parkinsonism, including SPs and tauopathies.
Methods: Patients with a syndromic diagnosis of degenerative parkinsonism matched for gender, age, and disease stage were assessed using a structured protocol with demographic and clinical data, including the diagnosis of probable RBD (pRBD), ascertained clinically using established criteria.
Results: One hundred cases of Parkinson's disease (PD), 87 with progressive supranuclear palsy (PSP), 72 with the parkinsonian form of multiple system atrophy (MSA), 50 with dementia with Lewy bodies (DLB), and 18 with corticobasal degeneration (CBD) were included. pRBD was found in 58 (58%) of the PD patients, 59 (81.9%) of those with MSA, 37 (74%) with DLB, 32 (36.7%) with PSP, and one (5.5%) with CBD. Among the SPs, pRBD was significantly more common in MSA when compared with PD patients. Differences were also significant individually for all SPs when compared to PSP. The positive predictive value (PPV) of pRBD for a SP was 82.3%, but sensitivity was 69.4% and specificity 68.6%.
Conclusions: In our sample, pRBD was more frequent in SPs than in PSP and CBD, however, its' frequency in PSP was significant. Although pRBD had a good PPV for a SP, all other measurements used for determine diagnostic performance were disappointing.

1. Introduction

Rapid eye movement (REM) sleep behaviour disorder (RBD) is a parasomnia in which patients physically act out their dreams. The behaviours may include vocalizations, grabbing, kicking, and jumping from the bed. Most of the enacted dreams have content that lead to violent behaviours and because of the nature of the actions, the potential for serious harm is significant. Population-based estimates of RBD prevalence are 0.5% among adults with a strong male predominance (up to 88%) [1].

RBD can be diagnosed clinically. The clinical diagnosis of RBD has been widely accepted, including screening tools that range from questionnaires to a single question with a yes or no answer, a screening method that has been validated demonstrating a sensitivity of 93.8% and a specificity of 87.2% [2]. From a polysomnographic standpoint, patients with RBD demonstrate lack of atonia during REM sleep, a finding that is very helpful to differentiate it from RBD mimics, that include sleep apnea, nocturnal seizures and parasomnias arising from non-REM sleep (such as somnambulism) [3]. As polysomnographic studies remain the gold standard, some authors recommend the caveat of designating the clinically based diagnosis as probable RBD (pRBD) [4].

Although RBD may occur as a primary disorder, the term "idiopathic" has indeed proven to be inaccurate as 40–65% of patients will turn out to develop into a neurodegenerative disorder, almost always a synocleinopathy (SP) [1]. The term SP designates a broad spectrum of neurodegenerative disorders that share the pathological finding of abnormal α-synuclein-immunoreactive inclusion bodies in neurons and/or macroglia [5]. Currently, this term includes Parkinson's disease (PD), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), the Lewy body variant of Alzheimer's disease, and neurodegeneration with brain iron accumulation type 1. PD, MSA and DLB are some of the most common degenerative differential diagnoses of parkinsonism. The other degenerative forms include the tauopathies,

* Corresponding author at: 399 Bathurst Street, ML-7 Toronto, ON, Canada M5T 2S8. Tel.: +1 416 603 6422.
E-mail address: renato.munhoz@uhn.ca (R.P. Munhoz).

http://dx.doi.org/10.1016/j.clineuro.2014.09.014
0303-8467/

another pathologically defined group of disorders that encompass progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [6].

Although the frequency of RBD in these tauopathies has been shown to be less significant, there is considerable questioning on whether its presence can be used as a clue to help the differential diagnosis in cases of degenerative parkinsonism [7,8]. Therefore, the objective of our study was to analyze the presence of pRBD in a large sample of patients with neurodegenerative parkinsonism and a clinically defined diagnosis, and also to estimate the utility and performance of this parasomnia as a determinant of the etiologic diagnosis.

2. Methods

We performed a cross-sectional study in patients with a syndromic diagnosis of degenerative parkinsonism, defined by the presence of least two out of four cardinal signs: rest tremor, rigidity, bradykinesia, and postural instability. All cases were followed at the State of Parana Parkinson Association, a large clinic dedicated for multidisciplinary care of patients with parkinsonism. Participants were only included in the study after a final diagnosis was established with the highest possible degree of clinical based certainty. In addition, cases had to be followed for at least 1 year and a minimum of three follow up visits. As RBD symptoms are more prevalent in males, with ageing, and more advanced disease, we matched all groups for these variables (gender, age and disease stage). Our review of the literature showed that disease duration is the least important of these items and, in fact, matching was impossible for PD and, on the opposite side of the spectrum, CBD after the other more relevant variables were matched. The matching process was performed initially for the cases with diagnoses different from PD, to find adequate means and ranges for the above mentioned variables. The cases of PD, which may have a broader variability for age and disease stage, were then selectively invited to enter the study, trying to match the three variables.

Data were collected by the same examiner, following a standardized protocol that included demographic and clinical data, as well as the diagnosis of pRBD. Patients were included only after their final diagnoses were established under the supervision of the senior author. We excluded those with a diagnosis of secondary parkinsonism, those with dubious or incomplete diagnostic criteria.

Groups were divided according to the final diagnosis, as PD, parkinsonian variant of MSA, DLB, PSP and CBD, which were defined using established criteria. All of which are listed on the reference section of this manuscript, are based on consensus criteria, and are widely used for clinical and research purposes [9–13]. Dopaminergic treatment parameters (responsiveness and occurrence of levodopa induced complications) were used to improve diagnostic accuracy, as established in each case. Brain MRI was performed for all subjects with atypical degenerative forms of parkinsonism. Disease stage was determined using the Hoehn & Yahr (H&Y) scale [14]. pRBD was ascertained clinically by the criteria proposed by the American Sleep Disorders Association, which does not require polysomnography [15]. This classification has been used and validated in recent studies on this parasomnia. pRBD was considered positive when the patients clinically fulfilled the essential criteria described in the International classification of sleep disorders manual: (i) movements related to dream content, and (ii) aggressive behaviour, dream "enactment" that may lead to injury and sleep disruption. The study was approved by the local ethic committee, all patients provided their informed consent.

2.1. Statistical analysis

Comparison of study findings among different parameters used the *t* test for means and the *chi* square test with Yates correction for continuity or Fisher exact test for categorical and ordinal data. Differences were considered significant for $p < 0.05$. Measurements of performance (sensitivity, specificity, positive and negative predictive values, and false positive rate) were calculated using the standard formulas.

3. Results

A total of 100 cases of PD, 87 of PSP, 72 of MSA, 50 of DLB, and 18 of CBD were included. Their demographic and clinical data are shown in Table 1, including frequencies of pRBD for each group. As previously outlined, groups were matched for variables that could bias our analysis. The process is shown in the supplementary table. Differences regarding disease duration were significant, therefore, not matched when any group was compared to PD and CBD, as already mentioned in Section 2. These differences were driven especially by the fact that matching disease duration in PD is particularly challenging when disease stage, a much more important variable in this specific situation, has been previously equalled. PD patients may take more than a decade to reach the same H&Y stage of a PSP or MSA patient with only a couple of years with each of these diagnoses. On the other hand, for comparisons between PSP, MSA, and DLB, this variable remained not significantly different. In the case of CBD, an even more aggressive disorder, the opposite effect was observed.

In regards to pRBD, all groups presented with a predominance of males: 41 (70.7%) for the PD group, 24 (75%) in PSP, 45 (76.2%) in MSA, and 29 (78.3%) in DLB groups. Specific group frequencies, comparisons as well as relative risks are presented in Tables 1 and 2. The one affected patient with CBD and pRBD was a female. In the group of patients with PD, 58 (58%) fulfilled proposed criteria for pRBD. These figures were even more robust for the other SP, reaching 59 (81.9%) of the 72 patients with MSA and 37 (74%) of those with DLB. Comparison of these relative frequencies among the different SPs shows that pRBD was significantly more frequent among patients with MSA when compared with PD patients. In addition, the relative odds of pRBD occurring in MSA were 3.29 compared to PD. Other comparisons among SPs did not reach statistical significance, although there was trend towards higher frequency in DLB

Table 1
Demographic and clinical findings of patients with parkinsonism.

	PD	PSP	MSA	DLB	CBD
n	100	87	72	50	18
Gender (male)	56 (56%)	52 (59.7%)	41 (56.9%)	28 (56%)	10 (55.5%)
Age (years)	72.6 ± 11.1	71.7 ± 7.6	70.3 ± 9.1	74 ± 6.2	72.3 ± 6.2
Onset (years)	62.2 ± 14	67.4 ± 7.6	65.2 ± 8.9	69.8 ± 6.6	69.3 ± 6.3
Duration (years)	10.6 ± 6.7	4.3 ± 1.9	4.1 ± 2.1	4.2 ± 1.9	3 ± 1
H&Y	3.8 ± 0.5	3.9 ± 0.6	3.8 ± 0.6	4 ± 0.6	3.9 ± 0.9
pRBD	58 (58%)	32 (36.7%)	59 (81.9%)	37 (74%)	1 (5.5%)

PD: Parkinson's disease; PSP: progressive supranuclear palsy; MSA: multiple system atrophy; DLB: dementia with Lewy bodies; CBD: corticobasal degeneration; pRBD: probable REM sleep behaviour disorder.

Table 2
Upper half of the table shows the *p*-value of the comparison of the frequencies of the diagnosis of pRBD among the parkinsonian disorders. Lower half of the table shows the relative risk for pRBD.

pRBD	PD	PSP	MSA	DLB	CBD
PD		0.006	0.0016	0.08	0.0001
PSP	2.37 (1.32 - 4.28)		< 0.0001	< 0.0001	0.02
MSA	3.29 (1.6 - 6.75)	7.8 (3.71 - 16.4)		0.4	< 0.0001
DLB	2.06 (0.98 - 4.35)	4.9 (2.27 - 10.54)	1.59 (0.67 - 3.88)		< 0.0001
CBD	23.48 (3 - 183.4)	9.9 (1.26 - 77.87)	77.1 (9.41 - 632.8)	48.4 (5.85 - 400.5)	OR (CI 95%)

PD: Parkinson's disease; PSP: progressive supranuclear palsy; MSA: multiple system atrophy; DLB: dementia with Lewy bodies; CBD: corticobasal degeneration; pRBD: probable REM sleep behaviour disorder; OR: odds ratio; CI: confidence interval.

when compared to PD with odds ratio of 2.06 but with the lower bounds of the confidence interval reaching 0.98.

Among the tauopathies studied, pRBD was less frequently detected: 32 (36.7%) out of 87 PSP patients and only one (5.5%) of the 18 cases of CBD. As shown in Table 2, all the above mentioned SPs had significantly higher frequencies of pRBD in comparison with those found for PSP, with relative odds this parasomnia occurring in PD, MSA and DLB ranging from 2.37 to 7.8 compared to the tauopathy. The positive predictive value, or in other words, the percentage of patients with any of the neurodegenerative disorders studied and pRBD who had, in fact, a SP was 82.3%. The negative predictive value was 51.4% with a false positive rate of 31.4%, while the sensitivity of pRBD was 69.4% and specificity was 68.6%.

4. Discussion

Our findings show that, although PD is considered as the prototype neurodegenerative disorder linked to pRBD, the other SPs studied, MSA and (probably) DLB, present with this parasomnia significantly more frequently. Also, we found that all forms of SPs studied present pRBD more frequently than the tauopathies analyzed, however, its' frequency in PSP was surprisingly high with more than one third of patients fulfilling the clinical criteria for pRBD. This finding justifies the fact that, although we found a relatively good positive predictive value for pRBD, the negative predictive value, sensitivity, and specificity analyses were disappointing. Our finding of one case of pRBD among CBD patients, make comparisons difficult to interpret, but probably points to lower frequencies among these cases, which is justifiable considering the topographic distribution of pathology in this specific disorder.

One of the studies that established the correlation between RBD and SPs was published more than 10 years ago. This study grouped clinical, polysomnographic and pathological data from 120 patients with SPs and 278 with tauopathies (Alzheimer's disease, frontotemporal dementia, PSP, and CBD) finding only 7 (2.5%) cases with pRBD, including one case positive with a diagnosis of PSP and CBD. In this study, the positive predictive value of RBD for a SP exceeded 90% [7]. More recently, the same group published a study with similar methodology but now extended to 172 pathologically confirmed cases, revealing equivalent findings [16]. Later, a polysomnographic study of patients with PSP found figures similar to the ones presented here, 35% versus 65% in matched PD patients. This study also showed that, in general, polysomnographic recorded sleep is more severely impaired in PSP than in PD, including a relatively high frequency of sleep-disordered breathing [8]. Interestingly, another study in patients with PSP with no pathological confirmation, but using polysomnography found strikingly similar results in regards not only to RBD but also to REM sleep without atonia [17]. On the other hand, Nomura et al. [18] demonstrated that, although REM sleep without atonia was diagnosed polysomnographically in 20% of their cases, none fulfilled clinical criteria for RBD, i.e., they did not enacted their dreams. These authors speculate that although the phenomenon of REM without atonia exists in PSP, it may not be correlated with RBD because PSP patients are less likely to have terrifying and uncomfortable dreams, which are considerably common in PD cases. Similarly, none out of 10 patients with PSP and only one out of 10 CBD cases was diagnosed with clinical pRBD in another study. Again, these authors described their findings as not surprising since these disorders do not have underlying alpha-synuclein pathology [19].

Our own findings as well as those of Sixel-Döring et al. [8] challenge the almost universal view of RBD been essentially pathognomonic of some form of SP, discarding a tauopathy. In our sample, although pRBD was significantly more common in PD or any of the SPs in comparison with PSP, its' presence in the referred tauopathy was appreciable, and not an odd finding as previously suggested. These data reinforce the notion that RBD may not arise from a specific molecular pathology, but rather from a topography-specific progression of the degenerative process. In the case of the SPs, these REM sleep regulation-related areas may be affected earlier and more consistently, but in fact, any pathological processes, either neurodegenerative or structural, that affect the brainstem, may be linked to RBD [20].

In regards to the relative occurrence of RBD among the SPs, a recent clinicopathologic study with 172 cases of RBD found that only two did not have an underlying neurodegenerative process, and among the 170 remaining, 94% had a SP [1]. Among them, another previous study demonstrated that MSA is probably the one more densely affected with RBD, about 90% of cases [21]. Another pathologic study utilizing the same pRBD criteria described here showed that 60% of cases with DLB had this parasomnia. This study also showed that the presence of pRBD was associated with a higher likelihood of a pathological diagnosis of DLB (diffuse neocortical Lewy bodies) and lower probability of finding Alzheimer-related pathology in the medial temporal lobes, whereas absence of pRBD was characterized by Alzheimer-like atrophy patterns on MRI and increased phospho-tau burden [22]. A polysomnographic study of patients with DLB showed occurrence of signs of pRBD in 70% of cases, however, 30% also presented with confusional events, which may represent another RBD-mimic [23]. Regarding its' relative importance in the differential diagnosis of dementia syndromes, Ferman et al. detected RBD in 75% of their patients with DLB, demonstrating that the addition of a non-polysomnographic based diagnosis of RBD improved significantly the sensitivity and specificity of currently used criteria for DLB [24]. Of importance, in regards to the differential diagnosis of dementia, RBD is not a feature of Alzheimer's disease and fronto temporal dementias [25]. Therefore, in cases of dementia, the positive predictive value of RBD is robust.

Our study has limitations: although the clinical diagnosis of RBD is generally acceptable for practical and research purposes, polysomnographic diagnosis remain as the gold standard. Also, we did not measure the intensity of the RDB symptoms or their relative

interference with sleep and other related parameters. Finally, our etiologic diagnoses for the parkinsonian syndromes were not confirmed pathologically. As such, the degree of diagnostic certainty of the sample studied here cannot be objectively determined. This may be particularly important in case of tauopathies, which may present with significant pathologic overlap. On the other hand, we systematically tried to substantiate our diagnoses by using established criteria that were confirmed by two movement disorders specialists.

In the cases of early parkinsonian syndromes with preserved cognition, differentiating MSA from PSP and PD may be challenging, especially when the emblematic "red flags" of the atypical cases may not be yet present or easily detectable clinically. In these situations, clinicians tend to rely more on the presence or absence of features that support, rather than exclude, the most common differential diagnosis, in this case PD [6]. Our study and others confirm that, in an adequate context, the presence of RBD in a parkinsonian patient increases odds of MSA by almost eightfold in comparison with PSP and by more than threefold in comparison with PD. However, we also demonstrate that RBD performs poorly as a classification parameter, with relatively low specificity and sensitivity.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clineuro.2014.09.014.

References

[1] Boeve BF. Idiopathic REM sleep behaviour disorder in the development of Parkinson's disease. Lancet Neurol 2013;12:469–82.
[2] Postuma RB, Arnulf I, Hogl B, Iranzo A, Miyamoto T, Dauvilliers Y, et al. A single-question screen for rapid eye movement sleep behavior disorder: a multicenter validation study. Mov Disord 2012;27:913–6.
[3] Frauscher B, Ehrmann L, Högl B. Defining muscle activities for assessment of rapid eye movement sleep behavior disorder: from a qualitative to a quantitative diagnostic level. Sleep Med 2013;14:729–33.
[4] Munhoz RP, Teive HA, Eleftherohorinou H, Coin LJ, Lees AJ, Silveira-Moriyama L. Demographic and motor features associated with the occurrence of neuropsychiatric and sleep complications of Parkinson's disease. J Neurol Neurosurg Psychiatry 2013;84:883–7.
[5] Takeda A, Mallory M, Sundsmo M, Honer W, Hansen L, Masliah E. Normal accumulation of NACP/α-synuclein in neurodegenerative disorders. J Pathol 1998;2:7–372.
[6] Munhoz RP, Werneck LC, Teive HA. The differential diagnoses of parkinsonism: findings from a cohort of 1528 patients and a 10 years comparison in tertiary movement disorders clinics. Clin Neurol Neurosurg 2010;112:431–5.
[7] Boeve BF, Silber MH, Ferman TJ, Lucas JA, Parisi JE. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. Mov Disord 2001;16:622–30.
[8] Sixel-Döring F, Schweitzer M, Mollenhauer B, Trenkwalder C. Polysomnographic findings, video-based sleep analysis and sleep perception in progressive supranuclear palsy. Sleep Med 2009;10:407–15.
[9] Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology 1992;42:1142–6.
[10] Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013;80:496–503.
[11] Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, et al. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 1999;163:94–8.
[12] Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996;47:1–9.
[13] McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. Neurology 2005;65:1863–72.
[14] Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–42.
[15] Diagnostic Classification Steering Committee. CSD-international classification of sleep disorders: diagnostic and coding manual. Rochester, MN: American Sleep Disorders Association; 1990.
[16] Arnulf I, Merino-Andreu M, Bloch F, Konofal E, Vidailhet M, Cochen V, et al. REM sleep behavior disorder and REM sleep without atonia in patients with progressive supranuclear palsy. Sleep 2005;28:349–54.
[17] Boeve BF, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med 2013;14:754–62.
[18] Nomura T, Inoue Y, Takigawa H, Nakashima K. Comparison of REM sleep behaviour disorder variables between patients with progressive supranuclear palsy and those with Parkinson's disease. Parkinsonism Relat Disord 2012;18:394–6.
[19] Cooper AD, Josephs KA. Photophobia, visual hallucinations, and REM sleep behavior disorder in progressive supranuclear palsy and corticobasal degeneration: a prospective study. Parkinsonism Relat Disord 2009;15:59–61.
[20] Dugger BN, Murray ME, Boeve BF, Parisi JE, Benarroch EE, Ferman TJ, et al. Neuropathological analysis of brainstem cholinergic and catecholaminergic nuclei in relation to rapid eye movement (REM) sleep behaviour disorder. Neuropathol Appl Neurobiol 2012;38:142–52.
[21] Iranzo A. Sleep and breathing in multiple system atrophy. Curr Treat Options Neurol 2007;9:347–53.
[22] Murray ME, Ferman TJ, Boeve BF, Przybelski SA, Lesnick TG, Liesinger AM, et al. MRI and pathology of REM sleep behavior disorder in dementia with Lewy bodies. Neurology 2013;81:1681–9.
[23] Terzaghi M, Arnaldi D, Rizzetti MC, Minafra B, Cremascoli R, Rustioni V, et al. Analysis of video-polysomnographic sleep findings in dementia with Lewy bodies. Mov Disord 2013;28:1416–23.
[24] Ferman TJ, Boeve BF, Smith GE, Lin SC, Silber MH, Pedraza O, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. Neurology 2011;77:875–82.
[25] Gagnon JF, Petit D, Fantini ML, Rompré S, Gauthier S, Panisset M, et al. REM sleep behavior disorder and REM sleep without atonia in probable Alzheimer disease. Sleep 2006;29:1321–5.